REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 4, 5, 16, 18, 19 and 21-40 are pending in this application. Claim 17 has been cancelled, claim 29 has been amended, and claims 39 and 40 have been added. Applicants reserve the right to pursue the subject matter of cancelled claims in continuing applications. No new matter has been added by this amendment.

Applicants thank the Examiner for withdrawing the finality of the previous Office Action. Applicants also thank the Examiner for indicating that the Declaration under 37 C.F.R. § 1.132 filed on January 21, 2004 is sufficient to overcome the Taylor reference, as well as any other reference that does not teach that two recombinant bovine vaccines can be used in combination.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. THE CLAIM OBJECTIONS ARE OVERCOME

Claim 17 was objected to under 37 C.F.R. § 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. Although the Applicants disagree, in the interest of expediting prosecution, claim 17 has been cancelled, thereby obviating the objection.

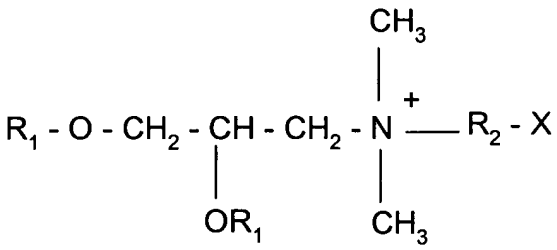
Claim 29 was objected to because it was believed the language of claim 29 could be clearer. Claim 29 has been amended as suggested by the Examiner on page 3 of the Office Action, thereby obviating the objection.

Reconsideration and withdrawal of the objections are requested.

III. THE DOUBLE-PATENTING REJECTIONS ARE OVERCOME

Claims 1, 4, 5, 16-19 and 21-38 were allegedly directed to an invention not patentably distinct from claims 1-13 of commonly assigned U.S. Patent No. 6,376,473 ("the '473 patent"). The rejection is traversed.

Claim 1 relates to the administration to a bovine or porcine of a combination vaccine, comprising (a) a combination of a cationic lipid containing a quaternary ammonium salt, of formula



in which R_1 is a saturated or unsaturated linear aliphatic radical having 12 to 18 carbon atoms, R_2 is another aliphatic radical containing 2 or 3 carbon atoms, and X a hydroxyl or amine group and a plasmid expressing an immunogen of a bovine or porcine pathogen and (b) a second vaccine, immunogenic, or immunological composition that is an inactivated, attenuated live, subunit or recombinant vaccine or immunogenic or immunological composition against a bovine or porcine pathogen.

Claims 1-13 of the '473 patent are directed to compositions and methods for inducing an immune response in a bovine wherein the composition comprises a plasmid that expresses BRSV-F and a second plasmid expressing BRSV-G. However, the claims of the '473 application do not encompass, nor do they render obvious, the administration of the DNA vaccine or immunogenic or immunological composition combined with the cationic lipid indicated above.

The Office Action admits that the '473 patent does not teach the addition of any other substances to the immunogenic composition. The Office Action alleges that all of the additional substances encompassed by the instant claims, including a cationic lipid, were known in the art as adjuvants that could increase the immunological response of a subject to an immunogen. Applicants respectfully disagree.

Furthermore, there is no teaching whatsoever in the '473 patent of adding the cationic lipid with the above-indicated formula to a plasmid containing and expressing a nucleotide sequence encoding an immunogen of a pathogen of the bovine or porcine. As indicated in the discussion below, selecting an adjuvant for a particular vaccine is per se inventive.

The composition of the '473 patent and the composition of the instant application are not the same composition. The instant claims require that the plasmid component of the composition to be combined with an adjuvant that is a cationic lipid of the indicated formula. This component is not taught or suggested, let alone required, by claims 1-12 of the '473 patent. Therefore, the claimed compositions are not the same.

Accordingly, the subject matter of this application and the '473 patent are patentably distinct, and reconsideration and withdrawal of the double patenting rejection are requested.

Claims 1, 4, 5, 16-19 and 21-38 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 84-118 of copending Application No. 09/760,574.

The issue of whether there is indeed double patenting is contingent upon whether new claims herewith are indeed considered and entered; and, if so, whether the Examiner believes there is overlap with claims ultimately allowed in the co-pending application. If, upon agreement as to allowable subject matter, it is believed that there is still a double patenting issue, a Terminal Disclaimer as to co-pending U.S. Application No. 09/760,574 will be filed.

Accordingly, reconsideration and withdrawal of the double patenting rejection, or at least holding it in abeyance until agreement is reached as to allowable subject matter, is respectfully requested.

Claims 1, 4, 5, 16-18, 21, 27, 28, 32, 33 and 36-38 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-13 of the '473 patent in view of Klavinskis et al. (1999). Claims 1 and 19 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-13 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135; IDS reference BF) and Baker (U.S. Patent No. 5,106,733). Claims 1, 5, 22, 25, 26 and 31 were rejected under the judicially created doctrine of obviousness-type double patenting

as allegedly being unpatentable over claims 1-13 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Li (WO 96/40945; IDS reference AL). Claims 1, 5, 23, 24, 29 and 30 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-13 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Choi et al. (Virology 1998, 250:230-240; IDS reference BS). Claims 1, 5 and 34 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-13 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135; IDS reference BF), Baker (U.S. Patent No. 5,106,733), Li (WO 96/40945; IDS reference AL) and Choi et al. (Virology 1998, 250:230-240; IDS reference BS). These rejections are addressed collectively and are respectfully traversed.

As stated above, there is no teaching or suggestion in the '473 patent to combine a DNA vaccine with cationic lipid containing a quaternary ammonium salt with the indicated formula. Furthermore, the Office Action admits that the '473 patent does not teach that the vaccine comprises a cationic lipid. However, the Office Action alleges that it would have been obvious to combine the '473 patent with Klavinskis.

It is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985). Applicants believe that only through the exercise of impermissible hindsight have the cited references been selected and relied upon by the Office. Applicants respectfully submit that there is no teaching or suggestion in the cited art to motivate one of ordinary skill in the art to combine elements of the references to result in the presently claimed invention.

Applicants respectfully point out that the selecting an adjuvant for a particular vaccine is per se inventive and not routine experimentation or optimization. In addition to the foregoing and the arguments of record, submitted herewith is a copy of the following articles, provided to show that one cannot extrapolate from the documents cited in the Office Action to assert that the instant invention is obvious, and to show teachings in the art away from the instant invention:

Edelman, "An Update on Vaccine Adjuvants in Clinical Trial," Aids Research and Human Retroviruses 8(8):1409-1411 (1992),

McElrath, "Selection of potent immunological adjuvants for vaccine construction," seminars in Cancer Biology 6:375-385 (1995),

Aucouturier et al., "Adjuvants designed for veterinary and human vaccines," Vaccine 19:2666-2672 (2001),

East et al., "Adjuvants for New Veterinary Vaccines," Chapter 1 in Progress in Vaccinology, vol. 4 Veterinary Vaccines, Springer Verlag, NY 1993, pp1-28,

Altman et al., "Immunomodifiers in Vaccines," Advances In Veterinary Science and Comparative Medicine 33:301-343 (1989), and

Wiilson et al., "Tissue Reaction and Immunity in Swine Immunized with *Actinobacillus pleuropneumoniae* Vaccines," Can J Vet Res 59:299-305 (1995).

The Examiner is respectfully requested to consider and make of record the herewith submitted articles, which are also cited on PTO-1449.

Edelman teaches that adjuvant use remains largely empiric. Edelman also teaches that adjuvant effects are unpredictable, with adjuvant results arising from a complex interplay between route of administration, timing of inoculations, antigen dose, host species, and within-species genetic variation. Thus, Edelman teaches that as a consequence of these variables, antigens are best matched with adjuvants by means of a trial by error process of iterative experiments, thereby showing that the extrapolation attempted in the Office Action is not consistent with the knowledge in the art, that the extrapolation attempted in the Office Action is not proper, and, that the extrapolation attempted in the Office Action is impermissible hindsight gleaned from the instant invention.

McElrath teaches that the success of an adjuvant in clinical studies may not always be predictable from animal studies, and that adjuvant properties may differ according to the immunogen with which the adjuvant is formulated (*See, e.g.,* Summary p 283). Thus, McElrath also shows that the extrapolation attempted in the Office Action is not consistent with the knowledge in the art, that the extrapolation attempted in the Office Action is not proper, and, that the extrapolation attempted in the Office Action is impermissible hindsight gleaned from the instant invention.

Aucouturier teaches that there are no universal adjuvants. Adjuvants must be adapted according to several criteria, such as the target species, the antigen, the type of immune response, *inter alia* (abstract, conclusion), further demonstrating that the extrapolation attempted in the Office Action is not consistent with the knowledge in the art, that the extrapolation attempted in the Office Action is not proper, and, that the extrapolation attempted in the Office Action is impermissible hindsight gleaned from the instant invention.

East provides that the mechanisms by which adjuvants promote the immune response are poorly understood. Indeed, East teaches that studies involving adjuvants still do not allow the skilled artisan to predict with confidence which adjuvant will work, particularly with recombinant vaccines, as the author directs that it is clear that, much more work needs to be done on the nature of immunopotentiation and adjuvant action before the skilled artisan can, with confidence, combine new generation antigens with appropriate adjuvants to make successful vaccines. (*See* Introduction p. 2, Conclusion, p. 17). East also shows that the extrapolation attempted in the Office Action is not consistent with the knowledge in the art, that the extrapolation attempted in the Office Action is not proper, and, that the extrapolation attempted in the Office Action is impermissible hindsight gleaned from the instant invention.

Altman discusses the hope for a universal vaccine formulation, in terms of optimal combinations of vehicles (which includes adjuvants, *see* p313), and notes that a universal vaccine formulation will not be available in the near future. Simply, examination of the vast literature in this area reveals that for almost every vehicle (including adjuvant) found to be effective with a given antigen and a certain vaccination schedule, a contrasting report documents the lack of activity by the same immunomodifier(s) with another antigen or under slightly different conditions (Concluding remarks page 338). Accordingly, the extrapolation attempted in the Office Action is not consistent with the knowledge in the art, that the extrapolation attempted in the Office Action is not proper, and, that the extrapolation attempted in the Office Action is impermissible hindsight gleaned from the instant invention.

And, Wiilson provides an example of trial with several adjuvants, showing that components known as an adjuvant (e.g., it has been effective as adjuvant in another setting), including the famous aluminium hydroxyde used in human vaccination, is not necessarily effective as an adjuvant in another setting (abstract), demonstrating that the extrapolation

attempted in the Office Action is not consistent with the knowledge in the art, that the extrapolation attempted in the Office Action is not proper, and, that the extrapolation attempted in the Office Action is impermissible hindsight gleaned from the instant invention.

In addition to the herein arguments and herewith literature, and the arguments of record, attention is respectfully directed to MPEP 2143.02 which provides that obviousness requires a reasonable expectation of success. As discussed herein and in the record, and through the literature herewith, there was no reasonable expectation of success of the instant invention prior to the present invention.

Furthermore, attention is directed to MPEP 2143 which mandates that the fact that references can be combined or modified is insufficient for an obviousness rejection; there must be some desirability in the art to modify reference teachings to arrive at an invention. In the present situation, as discussed herein and in the record, and through the literature herewith, there is no teaching, suggestion, incentive or motivation to modify the cited documents to arrive at the instant invention. In particular, the instant invention has two essential aspects: the first is that the plasmid vaccine is combined with a cationic lipid, which, as has been discussed during the prosecution of this application, provides significantly better results than administering a plasmid vaccine alone; the second is that the plasmid-lipid component is then combined with a "classical" (*i.e.* inactivated, attenuated live, subunit or recombinant) vaccine to create a multivalent composition. It is this combination of components that confers patentability to the instant invention. There is simply no motivation in the cited references to administer the combination of composition as the inventors have done.

It is submitted that when one considers all of the teachings in the art, and the mandates of the case law and the MPEP, it is clear that the rejections cannot stand. Accordingly, in view of the herein arguments and the accompanying references, reconsideration and withdrawal of the obviousness type double patenting rejections are respectfully requested.

IV. THE REJECTIONS UNDER 35 U.S.C. §103 ARE OVERCOME

Claims 1, 4, 5, 16-18, 21, 27, 28, 32, 33 and 36-38 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the '473 patent in view of Klavinskis et al. (1999). Claims 1 and 19 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999)

and further in view of Xiang et al. (Immunity 1995, 2:129-135; IDS reference BF) and Baker (U.S. Patent No. 5,106,733). Claims 1, 5, 22, 25, 26 and 31 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Li (WO 96/40945; IDS reference AL). Claims 1, 5, 23, 24, 29 and 30 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Choi et al. (Virology 1998, 250:230-240; IDS reference BS). Claims 1, 5 and 34 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135; IDS reference BF), Baker (U.S. Patent No. 5,106,733), Li (WO 96/40945; IDS reference AL) and Choi et al. (Virology 1998, 250:230-240; IDS reference BS). These rejections are addressed collectively and are respectfully traversed.

As stated above, there is no teaching or suggestion in the '473 patent to combine a DNA vaccine with cationic lipid containing a quaternary ammonium salt with the indicated formula. Furthermore, the Office Action admits that the '473 patent does not teach that the vaccine comprises a cationic lipid. However, the Office Action alleges that it would have been obvious to combine the '473 patent with Klavinskis.

Applicants wish to reiterate their position that the combination of the cited references does not provide the motivation to combine the components of the composition recited in the claims, nor does it provide the expectation of success. As has been discussed extensively, particularly in the Declaration under 37 CFR 1.132 by Dr. Jean-Christophe Audonnet submitted on January 21, 2004, none of the cited documents provides motivation to develop a method for obtaining an immunogenic response using (a) a cationic lipid and a plasmid expressing an immunogen of a bovine or porcine pathogen and (b) a second vaccine, immunogenic, or immunological composition that is an inactivated, attenuated live, subunit or recombinant vaccine, immunogenic, or immunological composition.

In addition to the non-obviousness arguments presented above, Applicants also respectfully direct the Examiner to Example 17 on page 65 to 67 of PCT Publication WO 01/5288. The Examiner is respectfully requested to consider and make of record the herewith

submitted PCT publication, which is also cited on PTO-1449. The data presented in Example 17 of PCT Publication WO 01/5288 presents the neutralizing antibody response of cattle immunized with plasmids expressing gB, gC and gD genes from bovine herpesvirus type-1 (BHV-1) in the presence or absence of DMRIE-DOPE. In the presence of DMRIE-DOPE, the neutralizing response is significantly higher than the neutralizing response in the absence of DMRIE-DOPE. Thus, the above data presents surprisingly superior results when a DNA vaccine is administered to an animal (e.g., cattle) in the presence of a cationic lipid (e.g., DMRIE-DOPE) as compared to administration of the DNA vaccine in the absence of a cationic lipid.

Accordingly, it is submitted that when one considers all of the teachings in the art, one does not find the motivation to combine the cited references, nor the expectation of success in doing so. Reconsideration and withdrawal of the Section 103 rejections are requested.

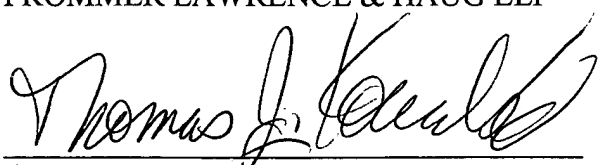
REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested; and, the Office Action is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 50-0320.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: 

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